canceled. Accordingly, claims 2-4 and 6-63 are pending. Claims 9-10, 14-26, 44-45, 50-51, 56-57 and 62-63 stand withdrawn from consideration as allegedly drawn to a non-elected species. Claims 2 and 3 have been amended to eliminate an unnecessary limitation. No new matter has been added.

Rejection under 35 U.S.C. § 102(b)

Claims 1-3, 5-7 and 35 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ruoslahti *et al.* (U.S. Patent No. 5,627,263, 1997) in the previous Office Action dated June 30, 2000. In particular, the previous Action asserted that Ruoslahti *et al.* taught a sequence CRGDSFVGC, comprising at least 5 or 7 consecutive amino acids of SEQ ID NO:1 (citing the entire reference, including Figure 3). In the present Action, the Examiner withdraws this rejection in view of Applicants' amendment to claims in response to the previous Action.

Applicants have amended claims 3 and 4 to eliminate the recitation "wherein Aaa is not glycine when Lys/Arg is arginine and Baa is aspartic acid" added in Applicants' amendment submitted in response to the previous Action. Applicants believe that currently pending claims 3 and 4 are patentable over the cited reference. Applicants' careful review of the entire reference has not identified the location where the sequence CRGDSFVGC is disclosed. Figure 3 is related to two peptides (*i.e.*, GACRGDCLGA and GACRRETAWACGA that do not comprise at least five or seven consecutive amino acides of SEQ ID NO:1. Figure 3 is not related to the peptide CRGDSFVGC.) Should the Examiner disagree, Applicants respectfully request the location where the sequence CRGDSFVGC is disclosed be specifically identified.

Claims 2, 35 and 40 are rejected under 35 U.S.C. § 102(b) as anticipated by Bult *et al.* (Science 273: 1058-73, 1996). In particular, the Action asserts that Bult *et al.* teach a 47mer protein that comprises the sequence IYSYX. In response to Applicants' arguments that the reference describes the entire genomic sequence of *Methanococcus jannaschii* and depicts many open reading frames and that there is no indication that the sequence is correct or that it is a functional open reading frame, the Examiner attaches a Genbank submission by Kohara (GenBank Acc. No. D64402, 1995) to support her statement that the genomic sequence is correct and functions in an open reading frame.

Applicants respectfully traverse this ground of rejection. The Genbank submission is an mRNA sequence of *Caenorhabditis elegans*. Applicants are unclear as to how this submission could prove that the genomic sequence of a different organism is correct and functions in an open reading frame. In addition, this submission, at most, indicates the nucleotide sequence is expressed in *C. elegans*. It does not provide information as to the amino acid sequence that the nucleotide sequence encodes because the nucleotide sequence itself does not contain the information as to the frame in which the nucleotide sequence is translated.

Accordingly, Applicants submit that this ground of rejection has been overcome. Withdrawal of this rejection under 35 U.S.C. § 102(b) is respectfully requested.

Rejection under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-4, 5-8, 11-13, 27-43, 46-49, 52-55 and 58-61 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. In particular, the Action asserts that the specification is not enabling for the current claim scope because it does not disclose the sequence identity of CAR containing peptides that actually reduce cell adhesion in the disclosed example, nor the 9 amino acid CAR sequence used to make the antibodies that have cell adhesion modulating activity as disclosed in Examples 2 and 4. Accordingly, the Action concludes that there is no clear guidance that an agent comprising SEQ ID NO:1 is capable of modulating claudin-mediated processes, such as cell adhesion. The Action further asserts that there is no predictability that the CAR sequence (based on an alignment with other mammalian claudins) would confer the biological activities such as cell adhesion to an agent comprising the CAR sequence because the specification does not disclose where the biological activity of cell adhesion of the claudin resides within SEQ ID NO:1.

Applicants respectfully traverse this ground of rejection. As pointed out in the amendment submitted in response to the previous Action and acknowledged by the Examiner, a specification is presumed enabling without evidence to the contrary. The Action makes the above assertions without evidentiary support. Accordingly, the Action has not fulfilled the initial burden of showing that one of ordinary skill in the art would reasonably doubt the disclosure. In the absence of such evidence, Applicants are not required to provide further evidence of the truth

of the disclosure, and a claim corresponding in scope to the disclosure of the specification must be taken to satisfy the enablement requirement.

Applicants respectfully submit that the present specification is enabling for the claimed invention. The claimed invention is directed to a cell adhesion modulating agent, or a composition thereof, comprising at least five, seven, or eight amino acid residues of a claudin CAR sequence having SEQ ID NO:1. A "claudin CAR sequence" is defined in the specification as an amino acid sequence present within a naturally occurring claudin and capable of detectably modulating a claudin-mediated function (*see, e.g.*, page 16, lines 28-30). The specification also discloses various assays to determine cell adhesion modulating activities of a particular agent (*see, e.g.*, page 39, line 27 to page 45, line 11). Given the teaching of the present application, one of ordinary skill in the art would be able to make and use the claimed invention through routine experimentation.

Accordingly, Applicants submit that this ground of rejection has been overcome. Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejection under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 2-8, 11-13, 27-43, 46-49, 52-55 and 58-61 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that is not adequately described in the specification. More specifically, the Examiner claims that even if the consensus sequence is adequately described, the specification does not provide adequate description of a claudin CAR sequence, specifically what set apart claudin sequences as a genus from those that are not claudin sequences.

Applicants respectfully traverse this ground of rejection. Applicants believe that the present specification provides adequate description of claudin sequences, and that in view of such description, one of ordinary skill in the art would be able to distinguish claudin sequences from those that are not. For instance, the specification defines the term "claudin as an integral membrane protein with a molecular weight of approximately 22 KD, which contains two extracellular domains and four transmembrane domains (as determined by hydrophobicity analysis) and which displays at least 30% sequence identity to a member of the claudin family specifically recited in the present application (*see, e.g.*, page 16, lines 12 to 16). The specification further provides exemplary members of claudin family, including claudin-1,

claudin-2, CPE-R and RVP-1 (*see, e.g.*, page 16, lines 16-24 and Figure 1). Given the above description, one of ordinary skill in the art would readily know whether a particular sequence is a member of claudin family.

Accordingly, Applicants submit that this ground of rejection has been overcome. Withdrawal of this rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 5 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite. More specifically, the Action states that the recitation of an agent comprising a peptide ranging in size from 3 to 50 amino acid residues is indefinite since claims 2-4 on which claim 5 depends encompass at least 5, 7 and 8 consecutive amino acid residues of SEQ ID NO: 1, respectively.

Applicants thank the Examiner for noting this informality and cancel claim 5 as claim 5 has the same scope as that of claim 2, 3 or 4. Accordingly, Applicants thus submit that this ground of rejection becomes moot and request its withdrawal.

New Ground of Rejection—Rejection under 35 U.S.C. § 112, First Paragraph

Claims 2-3, 5-8, 11-13, 27-43, 46-49, 52-55 and 58-61 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. More specifically, the Examiner asserts that there is no support in the specification or claims as originally filed for the recitation "wherein Ass is not glycine when Lys/Arg is arginine and Baa is aspartic acid."

Applicants respectfully traverse this ground of rejection. Without acquiescing in the Examiner's assertion, Applicants have deleted the above recitation because it is an unnecessary limitation to the present invention as discussed above. Accordingly, Applicants submit that this ground of rejection becomes moot and request its withdrawal.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made**."

Applicants respectfully submit that all claims in the application are in condition for allowance and request that the Examiner issue a Notice to that effect. If any issues remain

with regard to patentability, the Examiner is invited to telephone the undersigned at (206) 622-4900 to resolve these issues and place this application in condition for allowance.

Respectfully submitted,

Orest W. Blaschuk et al.

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Enclosures:

- Postcard
- Check
- Form PTO/SB/21
- Form PTO/SB/17 (+ copy)
- Petition for an Extension of Time

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Judib/176660

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

2. (Twice amended) A cell adhesion modulating agent that:

(a) comprises at least five consecutive amino acid residues of a claudin CAR sequence having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine~~, wherein Aaa is not glycine when Lys/Arg is arginine and Baa is aspartic acid~~; and

(b) contains no more than 50 consecutive amino acid residues present within the claudin.

3. (Twice amended) A cell adhesion modulating agent that:

(a) comprises at least seven consecutive amino acid residues of a claudin CAR sequence having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine~~, wherein Aaa is not glycine when Lys/Arg is arginine and Baa is aspartic acid~~; and

(b) contains no more than 50 consecutive amino acid residues present within the claudin.